CITATION 143885

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61P

A2

(11) International Publication Number: WO 00/61231

(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/GB00/01320

(22) International Filing Date: 7 April 2000 (07.04.00)

(30) Priority Data:
9907965.9 9 April 1999 (09.04.99) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BOUNTRA, Charanjit [GB/GB]; (GB). NOBBS, Malcolm, Stuart [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: FILLER, Wendy, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
*Without international search report and to be republished upon receipt of that report.*

(54) Title: MEDICAL USE

(57) Abstract

The present invention relates to the use of sodium channel antagonists the treatment of diseases mediated by, or exacerbated by, neuronal apoptosis, in particular sensory neuronal apoptosis.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# MEDICAL USE

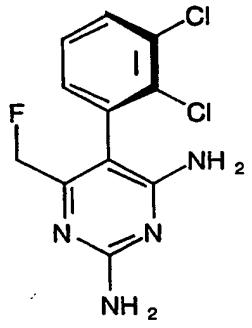
The present invention relates to the use of sodium channel antagonists for the treatment of diseases mediated by, or exacerbated by, neuronal apoptosis, in particular sensory neuronal apoptosis.

## Background to the Invention

EP-0021121-A discloses a group of 3,5-diamino-6-(substituted phenyl)-1,2,4-triazines which are active in the treatment of central nervous system (CNS) disorders, for example in the treatment of epilepsy. One such triazine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine which is alternatively called lamotrigine.

EP-0372934-A discloses pyrimidine compounds useful in the treatment of CNS disorders. Example 14 of this application discloses 5-(2,3-dichlorophenyl)-6-trifluoromethyl-2,4-diaminopyrimidine, Example 18 of EP-0372934-A discloses 2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and Example 45 discloses 5-(2,6-dichlorophenyl)-6-methyl-2,4-diaminopyrimidine.

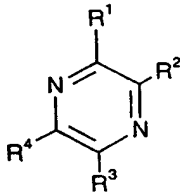
WO 97/09317 discloses the R(-) enantiomer of Example 18 of EP0372934-A, R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, substantially free of the corresponding S(+)enantiomer, ie the compound of formula (I):




(I)

and acid addition salts thereof. This compound is also known as 4030W92.

WO98/38174 discloses pyrazine derivatives useful in the treatment of CNS disorders such as epilepsy, ie the compounds of formula (II):




(II)

wherein

$R^1$ is selected from the group consisting of phenyl substituted by one or more halogen atoms, naphthyl and naphthyl substituted by one or more halogen atoms;

$R^2$ is selected from the group consisting of $-NH_2$ and $-NHC(=O)R^a$;

$R^3$ is selected from the group consisting of $-NR^bR^c$, $-NHC(=O)\ R^a$ and hydrogen;

$R^4$ is selected from the group consisting of hydrogen, -C $_{1-4}$ alkyl (preferably methyl), -C $_{1-4}$ alkyl (preferably methyl) substituted by one or more halogen atoms, -CN, $-CH_2OH$, $-CH_2OR^d$ and $-CH_2S(O)_xR^d$;

wherein

$R^a$ represents $C_{1-4}$ alkyl or $C_{3-7}$cycloalkyl, and

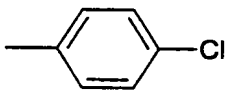
$R^b$ and $R^c$, which may be the same or different, are selected from hydrogen and $C_{1-4}$ alkyl, or together with the nitrogen atom to which they are attached, form a 6 - membered nitrogen containing heterocycle, which heterocycle can be further substituted with one or more $C_{1-4}$ alkyl;

$R^d$ is selected from $C_{1-4}$ alkyl or $C_{1-4}$ alkyl substituted by one or more halogen atoms;

x is an integer zero, one or two;

and pharmaceutically acceptable derivatives thereof;

with the proviso that $R^1$ does not represent;




when $R^2$ is $-NH_2$, and both $R^3$ and $R^4$ are hydrogen. Particularly preferred is 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine and pharmaceutically acceptable derivatives thereof.

WO99/32462 (PCT/EP98/08273) relates to a triazine compound which is useful in the treatment of central nervous system (CNS) diseases and disorders, ie the compound 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine and pharmaceutically acceptable derivatives thereof.

WO00/12488 relates to carboxamide derivatives of pyrazine compounds such as those disclosed in WO98/38174 above, in particular 5-carboxamido-2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine.

The compounds of EP-0021121-A, EP-0372934-A, WO 97/09317, WO98/38174 WO99/32462 and WO00/12488 are sodium channel antagonists and therefore inhibit glutamate release.

Other sodium ion channel blockers include local anaesthetics/anti-dysrhythmics such as: lidocaine, mexilitine, ropivacaine, levobupivacaine; anti-convulsants such as: oxcarbazepine, topiramate, rufinamide, Co-102862, NW-1015; anti-ischaemics such as: sipatrigine, BIIR-561, BIII-890 and RS100642 and the analgesics such as: RS132943, details for which are all available from public databases such as Pharmaprojects.

It has been shown that the sodium channel antagonist, lamotrigine can prevent motorneuronal apoptotic cell death after neonatal axotomy: Casanovas A. et al Neuroscience Vol.71 No2 pp313-325 1996.

## Summary of the Invention

This invention relates to a parallel finding of much greater medical significance, that as a result of their ability to prevent neuronal apoptosis, sodium channel antagonists have a disease modifying effect and serve to halt or delay (slow down) the progression of disease as opposed to merely treating the symptoms

of disease. For example, in the case of chronic pain, the sodium channel antagonists are able to halt or delay the underlying process which is causing the pain as well as ease the pain as demonstrated by behavioural testing. Thereby sodium channel antagonists can alter disease states in particular pain states mediated by sensory neuronal apoptosis. The ability to halt or delay the progression of disease states such as certain pain states, neurodegenerative diseases and inflammation, provides a significant breakthrough in the management of these otherwise poorly treated conditions.

Diseases mediated by, or exacerbated by neuronal apoptosis in particular sensory neuronal apoptosis, include: pain states, such as chronic pain states, following nerve insult due to, for example, injury or infection ie pain states associated with tissue damage; neurodegenerative diseases such as multiple sclerosis and Parkinson's disease; and inflammation. Sodium channel antagonists are of use in the treatment of these diseases and are also of use in delaying or halting the progression of these diseases.

It has previously been reported (see for example WO98/38186) that a deficiency of oxygen, for example in the region of a cerebral infarct, causes abnormally high concentrations of glutamic acid to be released. This leads to an over-stimulation of excitatory amino acid receptors, eg NMDA receptors, resulting in the degeneration and death of neurones by way of a mechanism known as excitotoxicity. This process has been implicated in the pathophysiology of various neurodegenerative conditions. Sodium channel antagonists are known to inhibit glutamate release and therefore prevent the degeneration and death of neurones due to excitotoxicity.

However, neuronal apoptosis which occurs as a result of nerve damage is unrelated to nerve death due to excitotoxicity and it is not dependent on glutamic acid concentration. "Apoptosis" is a form of programmed cell death. A report

from the Cell Death Nomenclature Committee (Apoptosis, Necrosis or Oncosis, Levin S. Toxicological Sciences 41 155-156 1998) defines the prelethal steps that follow cellular injury as apoptosis or oncosis (but not necrosis). Apoptosis is characterised by cytoplasmic shrinkage and karyorrhexis (The Pathways of Cell Death: Oncosis, Apoptosis and Necrosis Trump B.F. et al Toxicological Pathology 25 (1) 82-88 (1997) – chromatin is fragmented and packaged in bits of cell membrane. This shows up as densely coloured apoptotic bodies when visualised using a nuclear stain under the light microscope. Using electron microscopy the cytosol appears dense, endoplasmic reticulum may be dilated and mitochondria are condensed. Blebs in the cytoplasm will typically contain organelles. Breaks in the DNA that lead to karyorrhexis can be identified using gel electrophoresis or TUNEL staining but this alone is no longer considered adequate as cells stained positive using TUNEL, do not necessarily have the characteristics of apoptosis when studied at the electron microscopy level. The fluorescent nuclear stain Hoechst 33342 and light microscopic analysis is now considered the best technique. The most striking gross morphological characteristic is cell shrinkage.

As mentioned above, agents which prevent neuronal apoptosis have a disease modifying effect and serve to halt or delay the progression of disease.

The invention accordingly provides, in a first aspect the use of sodium channel antagonists in the treatment of diseases mediated by, or exacerbated by, neuronal apoptosis.

In a further aspect, the invention provides the use of sodium channel antagonists as disease modifying agents in diseases mediated by, or exacerbated by, neuronal apoptosis.

There is also provided as a further aspect of the invention the use of sodium channel antagonists in the preparation of a medicament for the treatment of diseases mediated by, or exacerbated by, neuronal apoptosis.

The invention has particular relevance in the case of sensory neuronal apoptosis and disease mediated or exacerbated by sensory neuronal apoptosis.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to neuronal apoptosis, comprising administration of an effective amount of a sodium channel antagonist.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to diseases mediated by, or exacerbated by, neuronal apoptosis, comprising administration of an effective amount of a sodium channel antagonist.

In a further aspect the invention provides the use of sodium channel antagonists in delaying or halting the progression of diseases selected from pain states following nerve insult, neurodegenerative diseases such as multiple sclerosis and Parkinson's, and inflammation.

In a further aspect the invention provides the use of sodium channel antagonists in the treatment of multiple sclerosis and inflammation.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Preferred sodium channel antagonists for use in the instant invention include those compounds included in EP-0021121-A, EP-0372934-A, WO 97/09317, WO98/38174, WO99/32462 and WO00/12488 , especially:

i) 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine called lamotrigine;

ii) R(-) and S (+) -2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine, called 4030W92 and 4082W92 respectively;

iii) 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine;

iv) 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine and pharmaceutically acceptable derivatives thereof;

v) (+/-) 5-(2,3-dichlorophenyl)-6-trifluoromethyl-2,4-diaminopyrimidine and

vi) (+/-)5-(2,6-dichlorophenyl)-6-methyl-2,4-diaminopyrimidine and their enantiomeric forms;

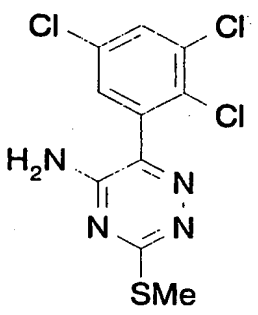
vii) 5- carboxamido-2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine.

Particularly preferred is R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, substantially free of the corresponding S(+)enantiomer.

Sodium channel antagonists may be prepared according to methods known in the art, for example according to the methods described in EP-0021121-A, EP-0372934-A, WO 97/09317, WO98/38174, WO99/32462 and WO00/12488.

5-Amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine may be prepared under suitable reaction conditions from a compound of formula (IIa)

9



(IIa)

for example, by reduction, preferably using a reduction metal, such as Raney nickel, and a source of hydrogen, such as hydrazine monohydrate, in a suitable solvent, such as ethanol, preferably at elevated temperature, for example between 70-75°C.

The compound of formula (IIa) may suitably be prepared by reacting 2,3,5-trichlorobenzoyl cyanide with a S-methylthiosemicarbazide salt, preferably hydroiodide, in the presence of a dilute mineral acid, preferably dilute sulphuric acid.

Other sodium ion channel blockers for use in the invention include compounds such as: lidocaine, mexilitine, ropivacaine, levobupivacaine; compounds such as: oxcarbazepine, topiramate, rufinamide, Co-102862, NW-1015; compounds such as: sipatrigine and BIIR-561, BIII-890 and RS100642; and compounds such as RS132943, details for which are all available from public databases such as Pharmaprojects.

Suitable dose ranges are as described in the art, eg as in EP-0021121-A, EP-0372934-A, WO 97/09317, WO98/38174, WO99/32462 and WO00/12488 . That is to say that for use according to the present invention the sodium channel antagonists may be used at doses appropriate for other conditions for which they are known to be useful. It will be appreciated that it may be necessary to make

routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A suitable dose range is for example 0.1 mg/kg to 30 mg/kg bodyweight per day calculated as the free base, for example 3 mg/kg to 15mg/kg. A suitable dose for an adult human is for example in the range of 200mg to 900mg per day.

The sodium channel antagonists may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art.

Description of the Drawings

Figure1. Numbers of neurones undergoing apoptosis in the naïve animal and at three time points after CCI surgery (7,21 and 30 days). Neuronal apoptosis is elevated up to 30 days post surgery.

Figure 2. The number of neurones undergoing apoptosis decreases when CCI animals (n=3 day 7, n=2 day 21, n=3 day 30 )are treated with the sodium channel blocker 4030W92 10 $mgKg^{-1}$ (crossed bars) and 4082W92 10 $mgKg^{-1}$ (slanted bars) (numbers per group as for vehicle timepoints) . Levels in the vehicle treated animals (solid bars) remained constant over the time course. In CCI animals at all time points there were significantly more apoptotic cells than in naïve animals (n=4) (hollow bar).

Description of the Detailed Embodiments

Example 1

Sodium channel antagonists have been shown to prevent neuronal apoptosis in the neonatal rat 1 and 3 days after sciatic nerve axotomy. Newborn animals received a single pre-emptive injection of R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, substantially free of the corresponding S(+)enantiomer (4030W92) (10 mg/kg, s/c). Twenty minutes later the animals were anaesthetised by hypothermia, the nerve exposed and transected at the mid thigh level. The extent of neuronal and glial apoptosis was investigated using the TUNEL technique combined with Hoechst 33342 (Sigma) and immunohistochemistry. The ipsilateral and contralateral L5 dorsal root ganglions were compared and the 4030W92 treated group was compared to vehicle treated controls and to animals that received an injection of 4030W92 alone, ie. no nerve transection. There was a significant reduction in the number of apoptotic neurons observed at 24 hours.

Example 2

Adult male random hooded rats were either chronic constriction injury (CCI) or sham operated at day 0. Dosing with vehicle, 4030W92 (10 mg/kg) or 4082W92 (10 mg/kg) was from day 12 to day 25. At time points 7, 14, 21, 27 and 30 days post surgery animals (n=3 per group except for naives) were sacrificed by exsanguination after behavioural testing as described below. Naïve animals were all sacrificed 30 days post surgery. L4 and L5 dorsal root ganglias were removed and placed in a freezing medium for sectioning. Sections (14μm) were cut using a freezing cryostat (Leica) and placed on poly (L) lysine coated slides. These were post-fixed in 4% paraformaldehyde (Sigma) for 20 minutes, dehydrated through alcohol and kept at –80° until required. On the day of staining, the sections were rehydrated through alcohol and placed in phosphate buffered saline (PBS) for at least 15 minutes. They were incubated with the fluorescent nuclear stain Hoechst 33342 (1μg/ml) (Sigma) for 4 minutes and

then washed extensively with PBS. After drying, the slides were mounted with Vectashield mounting medium (Vector Labs) and coverslipped. The slides could be kept in the dark for up to 6 weeks without fading.

The sections were studied under the microscope (Leica) at 400X for morphological signs of apoptosis – nuclear condensation, membrane blebbing and presence of apoptotic bodies (Trump 1997 *supra*). Cells were assigned as neurones or glia depending on their size, location, and general morphology. Four fields from each section were selected at random, the number of apoptotic cells and total number of cells was counted in each and then mean figures for each group were calculated. This analysis was carried out blind. The results are shown in Figures 1 and 2. It is clear from these results that CCI provides a suitable model of apoptosis following injury (Figure 1) and that the sodium ion channel blockers 4030W92 and 4082W92 significantly reduced sensory neuronal apoptosis at day 30 (Figure 2). Glial apoptosis was unaffected (results not shown).

Behavioural Test

Under isoflurane anaesthesia, the common left sciatic nerve of male Random Hooded rats (180-200g) was exposed at mid-thigh level. Four ligatures of chromic gut (4.0) were tied loosely around the nerve with a 1mm spacing between each. The wound was then closed and secured with suture clips. The surgical procedure was identical for the sham operated animals except the sciatic nerve was not ligated. The rats were allowed a period of seven days to recover from the surgery before behavioural testing began.

The effect on Chronic Constriction Injury-induced decrease in mechanical paw

withdrawal threshold was measured using an algesymeter (Randall LO, Selitto JJ. A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn. 1957; 61:409-419). In brief, from 7 days post surgery onwards every 2 or 3 days the animals were tested for mechanical hypersensitivity by applying an increasing weight (16 gram per second) to the dorsal surface of each hindpaw until the rat attempted to remove the paw. The increasing weight was halted at this point and the weight recorded and expressed as mechanical paw withdrawal threshold. The maximum weight applied in this model was 250 gram. Drug was administered once the hypersensitivity was maximal which in this case was at day 12.

The presence of mechanical allodynia was assessed using Von Frey Hair monofilaments (range:4.19-84.96g). The rats were lightly restrained and placed upon a metal grid floor. The monofilaments were applied to the plantar surface of the hindpaws from below the grid. The lowest monofilament to produce a withdrawal was the response recorded.

Administration of the sodium ion channel blockers 4030W92 significantly reversed the reduction in thresholds caused by CCI in these tests.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. The claims may take the form of product, composition, process or use claims and may include, by way of example, one or more of the following claims.

## Claims

1. The use of a sodium channel antagonist in the treatment of a disease mediated by, or exacerbated by, neuronal apoptosis.

2. The use of a sodium channel antagonist as a disease modifying agent in a disease mediated by, or exacerbated by, neuronal apoptosis.

3. The use of a sodium channel antagonist in the preparation of a medicament for the treatment of a disease mediated by, or exacerbated by, neuronal apoptosis.

4. The use of a sodium channel antagonist according to any of the preceding claims wherein the disease is mediated by, or exacerbated by, sensory neuronal apoptosis.

5. A method for the treatment of a mammal, including man, suffering from or susceptible to diseases mediated by, or exacerbated by, neuronal apoptosis, comprising administration of an effective amount of a sodium channel antagonist.

6. The use of sodium channel antagonists in delaying or halting the progression of diseases selected from pain states following nerve insult, neurodegenerative diseases and inflammation.

7. The use of a sodium channel antagonist in the treatment of multiple sclerosis or inflammation.

8. The use of the compound of formula (I) in the treatment of multiple sclerosis or inflammation.

Figure 1

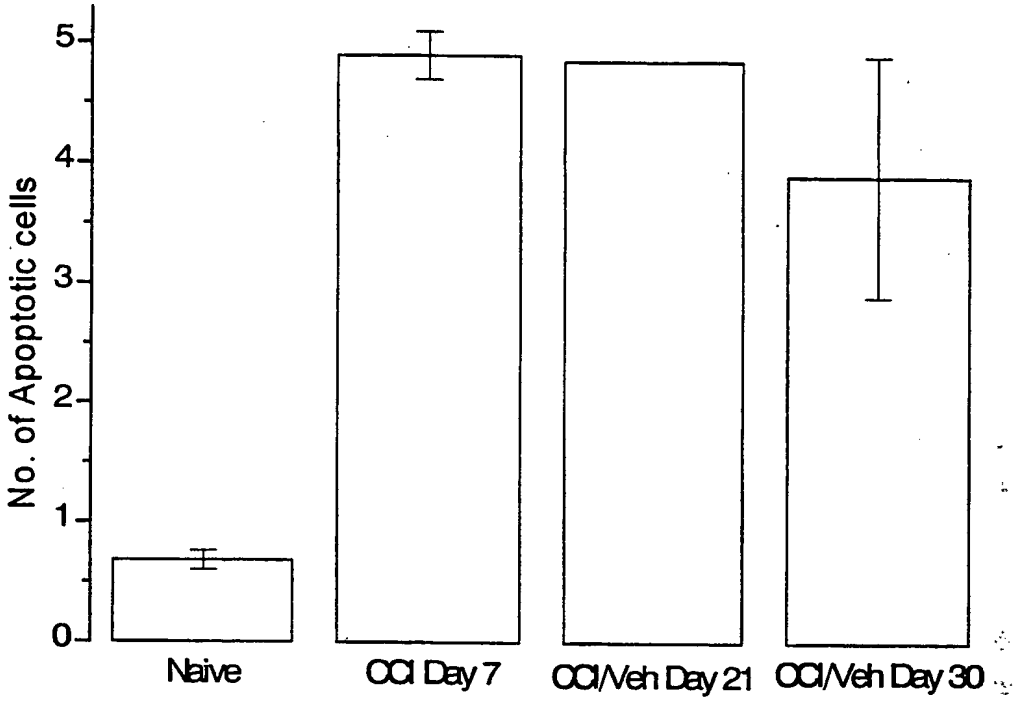
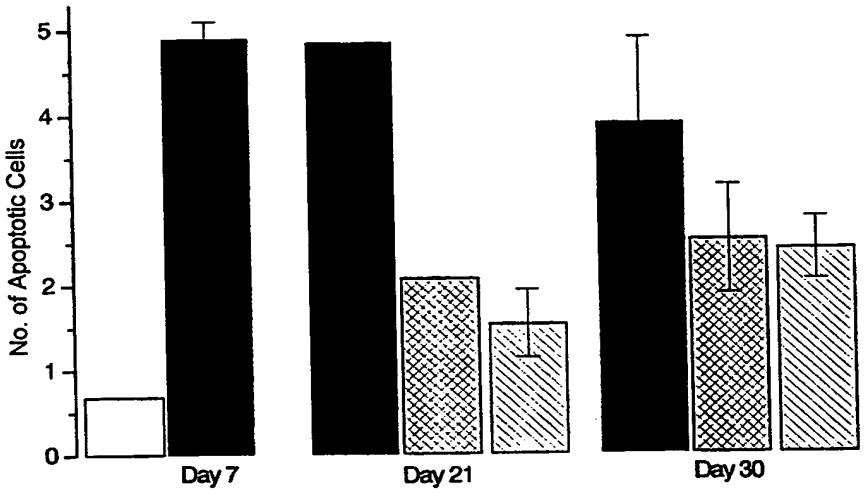

No. of Apoptotic cells
0
1
2
3
4
5
Naive
CCI Day 7
CCI/Veh Day 21
CCI/Veh Day 30

Figure 2



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 October 2000 (19.10.2000)

PCT

(10) International Publication Number
WO 00/061231 A3

(51) International Patent Classification[7]: A61K 31/53, 31/4418, 31/495, 31/4965, A61P 25/16, 25/28, 23/02, 25/04

(21) International Application Number: PCT/GB00/01320

(22) International Filing Date: 7 April 2000 (07.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9907965.9 9 April 1999 (09.04.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BOUNTRA, Charanjit** [GB/GB]; New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW (GB). **NOBBS, Malcolm, Stuart** [GB/GB]; New Frontiers Science, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **FILLER, Wendy, A.**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex, TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

(88) Date of publication of the international search report:
11 July 2002

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 00/061231 A3

(54) Title: MEDICAL USE

(57) Abstract: The present invention relates to the use of sodium channel antagonists the treatment of diseases mediated by, or exacerbated by, neuronal apoptosis, in particular sensory neuronal apoptosis.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01320

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/53 A61K31/4418 A61K31/495 A61K31/4965 A61P25/16
A61P25/28 A61P23/02 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 94 18972 A (WARNER LAMBERT CO)<br>1 September 1994 (1994-09-01)<br>* See Table 3, Lamotrigine *<br>claims 1,16<br>--- | 1-6 |
| X | CASANOVAS, A. ET AL: "Prevention by lamotrigine, MK-801 and N.omega.-nitro-L-arginine methyl ester of motoneuron cell death after neonatal axotomy"<br>NEUROSCIENCE (OXFORD) (1996), 71(2), 313-25,<br>XP000923487<br>page 320, column 1 -page 321, column 2; table 1<br>---<br>-/-- | 1-5 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 August 2000 | 22.12.00 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax. (+31-70) 340-3016 | Veronese, A |

2

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/GB 00/01320

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | MELDRUM, B. S. ET AL: "Sodium-channel blockade and glutamate release: The mechanism of cerebroprotection by lamotrigine, BW 1003C87 and BW 619C89" PHARMACOL. CEREB. ISCHEMIA 1994, [INT. SYMP.], 5TH (1994), 203-9. EDITOR(S): KRIEGLSTEIN, JOSEF;OBERPICHLER-SCHWENK, HEIKE. PUBLISHER: MEDPHARM SCIENTIFIC PUBLISHERS, STUTTGART, GERMANY., XP000925241 page 206, column 2 -page 207, column 2 --- | 1-5 |
| X | DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; MCCLEANE G: "Lamotrigine can reduce neurogenic pain associated with multiple sclerosis [letter]." retrieved from STN Database accession no. 1998429045 XP002144786 abstract & CLINICAL JOURNAL OF PAIN, (1998 SEP) 14 (3) 269-70., --- | 1-8 |
| A | EP 0 021 121 A (WELLCOME FOUND) 7 January 1981 (1981-01-07) the whole document ----- | 1-8 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/01320

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8 (partial)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8 (partial)

Use of lamotrigine in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple sclerosis, Parkinson' s disease, inflammation.

2. Claims: 1-8 (partial)

Use of R (-) and S (+) 2,4 diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine (called 4030W92 and 4082W92 respectevely), in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple sclerosis, Parkinson' s disease, inflammation.

3. Claims: 1-8 (partial)

Use of 2,6- diamino-3- (2,3,5-thrichlorophenyl) pyrazine in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple sclerosis, Parkinson' s disease, inflammation.

4. Claims: 1-8 (partial)

Use of 5-amino-6- [2,3,5-thrichlorophenyl] -1,2,4 triazine in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple sclerosis, Parkinson' s disease, inflammation.

5. Claims: 1-8 (partial)

Use of (+/-) 5-(2,3- dichlorophenyl)-6- trifluoromethyl -2,4 diaminopyrimidine in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple sclerosis, Parkinson' s disease, inflammation.

6. Claims: 1-8 (partial)

Use of (+/-) 5 -(2,6-dichlorophenyl) - 6 methyl -2,4-diaminopyrimidine in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

sclerosis, Parkinson' s disease, inflammation.

7. Claims: 1-8 (partial)

Use of 5- carboxamido-2,6- diamino -3-(2,3,5-thrichlorophenyl) pyrazine in relation to the treatment of diseases mediated or exacerbated by neuronal apoptosis selected among: pain states following nerve insult, multiple sclerosis, Parkinson' s disease, inflammation.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ ~~206~~ 210

Continuation of Box 3.

Although claims 1,2,4,5,6,7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

---

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

The wordings "The use of a sodium channel antagonist in the treatment of a disease mediated by, or exacerbated by, neuronal apoptosis" and the wording "The use of a sodium channel antagonist as a disease modifying agent in a disease mediated by, or exacerbated by, neuronal apoptosis" are obscure and render it difficult, if not impossible, to determine the matter for which protection is sought; for this reason, the present application fails to comply with the clarity and conciseness requirements of article 6 PCT.
Moreover, the wording "sodium channel antagonist" relates to compounds defined by reference to a pharmacological mechanism of action. The definition of compounds by reference to a pharmacological mechanism in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to fully compare the parameters the applicant has chosen to employ with what is set out in the prior art. In addition, present claim 1-8 relate to a rather elevated large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely for the compound lamotrigine, with due regard to the general idea underlying the application.

Claims searched incompletely: 1-8

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# IN RNATIONAL SEARCH REPORT

Information on patent family members

Inter. onal Application No
PCT/GB 00/01320

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9418972 A | 01-09-1994 | US 6133299 A | 17-10-2000 |
| | | AU 6269594 A | 14-09-1994 |
| EP 0021121 A | 07-01-1981 | AR 227521 A | 15-11-1982 |
| | | AT 370097 B | 25-02-1983 |
| | | AT 289680 A | 15-07-1982 |
| | | AU 566870 B | 05-11-1987 |
| | | AU 530999 B | 04-08-1983 |
| | | AU 5890680 A | 04-12-1980 |
| | | BG 60427 B | 31-03-1995 |
| | | CA 1112643 A | 17-11-1981 |
| | | CA 1133938 A | 19-10-1982 |
| | | CS 234018 B | 14-03-1985 |
| | | CZ 9103848 A | 13-10-1993 |
| | | DD 151309 A | 14-10-1981 |
| | | DE 3063084 D | 16-06-1983 |
| | | DE 3071000 D | 19-09-1985 |
| | | DK 233880 A,B, | 02-12-1980 |
| | | EP 0059987 A | 15-09-1982 |
| | | ES 491998 D | 16-05-1981 |
| | | ES 8104993 A | 01-08-1981 |
| | | FI 801758 A,B, | 02-12-1980 |
| | | FI 840888 A,B, | 06-03-1984 |
| | | GR 68380 A | 28-12-1981 |
| | | HU 182086 B | 28-12-1983 |
| | | IE 49823 B | 25-12-1985 |
| | | IL 60201 A | 31-05-1984 |
| | | IT 1147087 B | 19-11-1986 |
| | | JP 1044706 B | 29-09-1989 |
| | | JP 1567898 C | 10-07-1990 |
| | | JP 56025169 A | 10-03-1981 |
| | | JP 1044179 B | 26-09-1989 |
| | | JP 1569585 C | 10-07-1990 |
| | | JP 61033163 A | 17-02-1986 |
| | | LT 2066 R | 15-06-1993 |
| | | LV 5246 A | 10-10-1993 |
| | | MX 9202962 A | 01-07-1992 |
| | | MY 6285 A | 31-12-1985 |
| | | NZ 193890 A | 06-07-1984 |
| | | NZ 198159 A | 09-11-1984 |
| | | PL 224633 A | 13-02-1981 |
| | | SU 1055331 A | 15-11-1983 |
| | | US 4486354 A | 04-12-1984 |
| | | US 4602017 A | 22-07-1986 |
| | | YU 145680 A | 28-02-1983 |
| | | ZA 8003250 A | 27-01-1982 |
| | | ZW 12980 A | 06-01-1982 |